Remarks

Claims 1-8 are under consideration. Claims 1-8 have been amended. Claims 9-11 have been cancelled. Reconsideration of claims 1-8 is respectfully requested.

35 U.S.C. § 112, first paragraph

The Action rejects claims 1 and 2 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because there is no way to ensure that two independent laboratories would necessarily generate the exact same ES cells. The Action requires that the cell lines described in the specification and in the claims be deposited under 37C.F.R. 1.801-1.809.

In response, applicants disagree, because the biological materials and their preparation have been adequately described so that for one skilled in the art, the disclosure would be sufficient to meet the enablement requirement under 35 U.S.C 112. However, applicants have deposited two C57 ES cell lines- IC1 and IAC1- with American Type Culture Collection, P.O.Box 1549, Manassas, VA 20108, (at the cost of $2500/cell line). A copy of the BUDAPEST TREATY DEPOSIT FORM (BP/1) is enclosed. A Copy of the Certificate of Deposit and Viability will be submitted subsequently.

The Action rejects claims 3-11 because the specification is found to be enabling for a mouse and not for a non-human vertebrate animal. Similarly claim 4 is rejected because the specification is found to be enabling only for transgenic mice limited to specific mouse cell lines described and not to a non-human animal.

In response, Applicants have amended claims 3-8 (and cancelled claims 9-11) without admitting that the present specification is not relevant to non-human vertebrate animals and non-human animals. Therefore amended claims 3-8 should be allowed.

35 U.S.C. § 112, second paragraph

Claim 3 is rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

In response, claim 3 is amended to more specifically indicate a method for generating a transgenic C57 mouse by introducing C57 ES cells with marker genes into blastocysts from the same color strain, and then transplanting the blastocysts into a pseudopregnant animal of the same or different color. This method will greatly improve the efficiency of producing genetically modified C57 mice. See Declaration of Dr. Wei He, Section # 4.

35 U.S.C. § 102

The Action states that claims 1 and 2 are rejected under 35 U.S.C. 102 (b) as being anticipated by Tarrant et al. (2002, Mol. Cell Biol 22:5006-5018).

In response, applicants disagree. Tarrant et al teach ES cells derived from 129/Sv.C3^{-+c+p} inbred mice which are injected into BALB/c blastocysts, i.e ES cells from a different strain of mice from mice from which the blastocysts were taken. Tarrant et al does not teach how to isolate ES cells from C57 and definitely does not teach injecting black C57 ES cells into black C57 blastocysts ("black in black").

Amended claims 1 and 2 specifically encompass C57 ES cell lines that are distinguishable from Tarrant et al's. . Support for claims 1 and 2 is described in the present specification.

For a reference to qualify as anticipatory, the reference must have each and every element of the invention being claimed. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly of inherently described, in a single prior art reference" Verdegaal Bros. v. Union Oil Co of California, 81 F2d 628, 631, 2 USPQ 1051, 1053 (Fed Cir 1987).

Therefore the rejection of claims 1 and 2 should be withdrawn.

The Action rejects claim 3 as being anticipated by Schuster-Gossler, et al., (2001, BioTechniques 31: 1022-1026), because the reference demonstrates that mosaic male mice (of the C57BL/6J line) are bred to coisogenic female mice (of the C57BL/6J-Tyr $^{c-2J}$ line) and generate genetically modified progeny.

In response, applicants disagree. Shuster-Gossler describes a "black into white" chimerism, and introduces the tyrosinase mutation which has to be taken out by mating and genotyping, which introduces more steps. Moreover, in Schuster-Gossler, the blastocyst production is low in white B6 strain, which is a disadvantage. See page 1026, last paragraph. Therefore, amended claim 3 is not anticipated by Schuster-Gossler, and this rejection should be withdrawn.

The Action rejects claims 4 and 5 as being anticipated by Clouthier et al. (1998, Development, 125:813-824) that describes a method of making transgenic mice via ES cells.

In response, applicants disagree because Clouthier et al describe a procedure using different strains of mice, In Clouthier et al, homologous sequences for the ET_A gene were from an EMBL3 mouse genomic library, and the ES cells are from a different strain (JH-1 ES Cells maintained on SNK76/7 feeder layers). Correctly targeted ES clones were injected into blastocysts from C57BL/6 mice to obtain chimeras. See page 814, Materials and Methods. JH-1 ES cells were derived from the 129 mouse strain. See Hosada et al. 1994. Moreover, the chimerism in Clouthier et al was identified by coat color.

In the present invention a new method is used for identifying the chimerism of chimeras to determine how the ES cells contribute to the host blatocysts. See Declaration of Dr Wei He, Section 4.

For a reference to qualify as anticipatory, the reference must have each and every element of the invention being claimed. Therefore, as a matter of fact and law, amended claims 4 and 5 should be allowed.

35 U.S.C. § 103

The Action rejected claims 1-11 under 35 U.S.C. 103 (a) as being unpatentable over Schuster-Gossler, et al (2001, BioTechniques, 31:1022-1026) in view of Wei (1997, Annu. Rev. Pharmacol. Toxicol., 37: 119-41).

The Action states that Schuster-Gossler et al teach that efficient production of gene-targeted mice has not been met. The Action outlines the methodology described in

the reference, and concludes that the reference does not teach how to make transgenic mice.

Regarding Wei, the Action states that this reference teaches that microinjection of purified DNA into the pronuclei of fertilized one-cell eggs (transgenesis) and while problems of random integration were encountered a technique was developed that can deliver a single copy of a mutated gene to a specific target site. Therefore, the Action concludes that it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Schuster-Gossler and Wei and use mice with a different genetic background than the ones commonly used in transgenic studies (129-derived line).

Applicant disagrees. Under Graham v. John Deer Co. in the consideration and determination of obviousness under 35 U.S.C. § 102, four factual inquiries have to be made:

i. Determining the scope and contents of the prior art;

ii. Ascertaining the differences between the prior art and the claims in issue;

iii. Resolving the level of ordinary skill in the pertinent art; and

iv. Evaluating evidence of secondary consideration.

The following tenets of patent law must be adhered to:

i. The claimed invention must be considered as a whole;

ii. The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

iii. The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

"In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious" Stratoflex Inc. v. Aeroquip Corp., 713 F. 2d 1530, 218 USPQ 871 (Fed Cir 1983).

"[A] patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the subject matter as a whole, which should be considered in determining the obviousness of an invention under 35 U.S.C. § 103" In re Sponnoble 40S F 2.2d 578, 585, 160 USPQ 237, 243 (CCPA 1969).

In the present invention, applicants have overcome the disadvantages and problems encountered by Schuster-Gossler et al of low blastocyst production in the C2J strain. Applicants discovered the source of the problem causing inefficient germline transmission and production of chimeric mice. Whereas, Schuster-Gossler et al describes a "black into white" chimerism, applicants used a new approach to demonstrate chimerism of chimeras by injecting black B6 ES cells into black B6 blastocysts ("black in black"). Another disadvantage of Schuster-Gossler et al.'s method was the introduction of the tyrosinase mutation which has to be taken out by mating and genotyping, which introduces more steps. See Declaration of Dr Wei Hei, section 4.

There is no teaching or suggestion in Schuster-Gossler et al to combine the teachings of Schuster-Gossler and Wei and use mice with a different genetic background than the ones commonly used in transgenic studies (129-derived line). Hindsight afforded by the present invention is impermissible under Graham.

Therefore, as a matter of fact and law, the rejection of claims 1-8 should be withdrawn.

If for any reason, the Examiner should deem this application not in condition for allowance, the Examiner is respectfully requested to telephone the undersigned attorney to resolve any outstanding issues prior to issuing a further Office Action in the interest of moving the prosecution forward efficiently.

Respectfully Submitted,

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January 18, 2005.

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January 18, 2005.

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I hereby certify that this correspondence is transmitted by Express Class No. ED 096541875 US under 37 C.F.R. 1.10 on January 18, 2005 addressed to: Commissioner for Patents, Alexandria, VA 22313-1450.

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1/18/2005